REMARKS

Claims 7, 20, 21 and 28-39 are pending. All pending claims stand rejected under 35 U.S.C. § 102 and/or 35 U.S.C. § 103, based upon newly cited prior art references. Claims 21, 31, 32, 34, and 35 have been amended; no new matter is added by the amendments.

Admission of these claim amendments after final is respectfully requested. The amendments do not enlarge the scope of the claims and therefore do not require a new search or raise new issues for consideration. The amendments merely serve to place the claims in a condition for allowance, and address comments made by the Examiner in Paper No. 14.

The Examiner's rejections and comments are addressed in the order they were set forth in Paper No. 14.

I. Rejection Under 35 U.S.C. § 102(b) as Anticipated by U.S. Patent No. 4,254,129

The Examiner has rejected claim 34 under 35 U.S.C. § 102(b) as anticipated by the disclosure of U.S. Patent No. 4,254,129 of Carr, *et al.* ("Carr"). In support of the rejection, the Examiner argues that Carr teaches a composition having 0.01 to 20 md/kg of body weight of piperidine derivative and a carrier. The Examiner asserts that Carr discloses fexofenadine because it is a piperidine derivative, and that Carr teaches a carrier propylene glycol or polyethylene glycol. The applicants respectfully traverse the rejection.

Carr discloses substituted piperidine derivatives of the general structure represented by Formula 1 (col. 1, lns. 35-59). Carr also teaches that the compounds of the invention may be administered in injectable dosages by solution or suspension of the compounds in the physiological acceptable diluent with a pharmaceutical carrier. Carr suggests that the carrier for the injectable dosage may be a sterile liquid such as water, saline, aqueous dextrose, and related sugar solution, and glycols, such as propylene glycol or polyethylene glycol.

Carr does not teach each element of the invention. In particular, the Carr reference does not disclose a composition containing a compound having the same structure of fexofenadine or a pharmaceutically salt thereof, and propylene glycol as a carrier for administration to the eye or nose. None of the examples, or other combinations teaches this specific composition for

administration to the eye or nose or otherwise. Accordingly, the Carr patent does not anticipate the invention as claimed.

It is respectfully requested that the Examiner reconsider and withdraw the rejection.

II. Rejection Under 35 U.S.C. § 102(b) as Anticipated by European Patent 0 468 392 of Conte, *et al.* or WO 94/16733 of Chiesi, *et al.*

The Examiner has rejected claims 28, 29, 34, 35, 37 and 38 under 35 U.S.C. § 102(b) as anticipated by European Patent 0 468 392 of Conte, *et al.* ("Conte"). As basis for the rejection, the Examiner argues that Conte discloses a pharmaceutical composition comprising terfenadine, beta-cyclodextrin, hydroxy propyl methyl cellulose, and that the amount of terfenadine present is about 23%.

Similarly, the Examiner has rejected claim 34 under 35 U.S.C. § 102(b) as being anticipated by WO 94/16733 of Chiesi, *et al.* ("Chiesi"). The Examiner argues that Chiese discloses a composition comprising terfenadine and cyclodextrin.

The applicants respectfully traverse each of these rejections, for neither of the references asserted under § 102(b) teaches all elements of the claim.

Conte describes a process for preparing pharmaceutical compositions by co-grinding or dry mixing an active substance with cyclodextrins or with hydrophilic polymer materials. The active ingredients described in Conte include naftazone, terfenadine, carbamazepine, gliclazide, glibenclamide, bifonazole, nifedipine, diazepam, and ketoprofen. See page 4, lines 4-6. Conte does not disclose use of fexofenadine.

Similarly, Chiesi describes highly soluble multi component inclusion complexes that include a basic drug, a cyclodextrin, and requires an acid. In the examples of Chiesi, the drugs used in the inclusion complexes are terfenadine, domperidone, and astemizole, tamoxifene, ketoconazole, clomifene, cylcobenzaprine, itraconazole. Chiesi is silent on the use of fexofenadine in the inclusion complexes.

In contrast, the present invention is directed to compositions including fexofenadine or a pharmaceutically acceptable salt of fexofenadine and a pharmaceutical excipient that is selected from a cylcodextrin, propylene glycol, and glycolfurol, and methods of treating a patient in need or of treating rhinitis including administering an effective amount of these compositions. The

invention includes the drug fexofenadine, not terfenadine. Contrary to the Examiner's assertion, fexofenadine is not the same chemical compound as terfenadine, and does not exhibit the same behaviors when complexed with other compounds or placed in solution. *See, e.g.* Declaration of Peter James Watts, enclosed herewith; see also The Merck Index, 11th ed., at 1443.

Terfenadine is α-[4-(1, 1-dimethylethyl)phenyl]-4-(hydroxydiphenylmethyl)-1-piperidine butanol having the empirical formula $C_{32}H_{41}NO_2$. Fexofenadine and its salts are of a different structure having an empirical formula $C_{32}H_{39}NO_4$ or $C_{32}H_{39}NO_4 \cdot X$, where X is, *e.g.*, HCl. *Compare* Specification at 2 (showing the molecular structure of fexofenadine hydrochloride) and The Merck Index, 11 ed. At 1443 (showing the molecular structure of terfenadine).

Accordingly, neither Chiesi nor Conte teaches each element of the invention as claimed; therefore neither anticipates the claims. It is requested that the Examiner reconsider and withdraw the § 102 anticipation rejections based upon Chiesi and upon Conte.

III. Rejections Under 35 U.S.C. § 103

The Examiner has rejected claims 7, 20, 21, 30-33, 36 and 39 under 35 U.S.C. § 103(a) as being obvious over Conte combined with one of three secondary references: (i) Chiesi, (ii) U.S. Patent No. 5,646,131 of Badwan, *et al.* ("Badwan"), or (iii) WO 97/02017 of Clancy, *et al.*

Specifically, the Examiner argues that claims 7 and 13 are obvious in view of the combination of Conte with Chiesi. The Examiner relies on Conte as applied in the anticipation rejection, and further asserts that Chiesi provides a teaching that terfenadine can be formulated with hydroxypropyl beta-cyclodextrin to enhance solubility.

Claims 20, 21, 31, and 32 stand rejected as being unpatentable over Conte (as applied in the anticipation rejection) combined with Badwan for, as the Examiner concedes, Conte is silent on the administration of the Conte composition to a person suffering from rhinitis. The Examiner asserts that Badwan teaches a composition comprising terfenadine and cyclodextrin that is administered to a person suffering from rhinitis.

The Examiner rejected claims 30, 33, and 39 as obvious in view of the combination of Conte (as applied in the anticipation rejection) with Clancy. The Examiner concedes that Conte does not teach a composition containing terfenadine and a poloxamer block copolymer but

asserts that Clancy discloses a method of formulating terfenadine with a hydrophilic poloxamer block copolymer to prepare a sustained release composition.

The applicants traverse each of these rejections, for none of the three combinations asserted by the Examiner exhibits a *prima facie* case of obviousness.

A. The Examiner Has Failed to Make A *Prima Facie* Case of Obviousness

The disclosures of Conte and Chiesi are discussed above in the anticipation section of this response.

Badwan teaches a method for enhancing the solubilization and/or complexation of a drug that includes combining the drug with a cyclodextrin and a hydroxycarboxylic or a polycarboxylic acid. In Badwan, the drugs used in the composition are NSAIDs, terfenadine and cinnarizine, vasodilators, oxytoxic agents and abortifacients, sedatives, tranquilizers, hypnotics, anti-convulsants, anxiolytics, muscle relaxants, and anti-spasmatics. Col. 4, ll. 40-61. Badwan does not teach use of fexofenadine. Moreover, the Badwan combination requires that the selected α, β, or γ-cyclodextrin and the selected drug are combined in the presence of a selected poly-functional acid component, in order for the desired increase in solubility to be manifest. *See, e.g.*, col. 5, lns. 19-33.

Clancy describes a controlled release formulation for oral administration that includes a solid dispersion of an active ingredient in a hydrophilic poloxamer. The solid dispersion is a component of a core. The core is enclosed in a polymeric coating that allows for attachment of therapeutic levels of the active ingredient over extended periods of time following oral administration. Clancy teaches that active ingredients for use in the controlled release formulation include cisapride, cyclosporin, diclofenac, felodipine, ibuprofen, indomethacin, nicardapine, nifedipine, terfenadine, and theophylline. *See* page 5. No disclosure of fexofenadine is provided. Clancy is specifically concerned with producing compositions suitable for controlled drug release following oral administration. Page 7, lines 17-23. There is nothing in Clancy suggesting that it could be used for controlled release of a drug administered via the nose or eye.

The combinations put forth by the Examiner of Conte-Chiesi, Conte-Badwan, and Conte-Clancy each do not render the claims obvious, for none of the combinations teach or suggest

each element of the claims. First, as discussed above in the anticipation section of this response, Conte does not teach or suggest use of fexofenadine as an active ingredient. All describe compositions containing various active ingredients, such as terfenadine. None of the secondary references remedy the deficiency of Conte as none of Chiesi, Badwan, or Clancy teaches use of fexofenadine.

Moreover, the Examiner has failed to demonstrate that there would have been any motivation of a person of skill in the art to make any of the three suggested combinations, or that the person would have had a reasonable expectation that such combinations would result in a successful controlled release formulation for administration to the eye or nose. One of skill would not have been motivated to combine Conte with Chiesi for there is no teaching in either Conte or Chiesi that suggests that any cyclodextrin, including hydroxypropyl-beta-cyclodextrin, could be used to improve the solubility of fexofenadine. Each of Conte and Chiesi describes, *inter alia,* compositions containing terfenadine.

Similarly, the Examiner has not established a motivation for the combination of Conte with Badwan. Badwan describes a method for enhancing the solubilization and/or complexation of a drug with cyclodextrin. Badwan suggests that one drug for use in the Badwan composition is terfenadine. However, as Badwan does not teach or address use of fexofenadine, Badwan does not provide any motivation that would have provoked a person of ordinary skill to attempt to improve the solubility of fexofenadine using a cyclodextrin. Additionally, as Badwan is silent on the use of fexofenadine, a person of ordinary skill could not have had any reasonable expectation that the combination would be successful. To the contrary, Badwan teaches away from the combination of it with Conte, as Badwan suggests that the use of an acid is essential to enhance the solubility of drugs when combining them with a cyclodextrin. In the present invention, the presence of an acid is not necessarily required.

Still further, it should be noted that the teachings of Badwan are concerned with providing compositions in the form of non-alcoholic syrups and fast-dissolving tablets, capsules, effervescent tablets and/or sachets. All of these compositions are obviously intended for oral administration. There is nothing in Badwan that would have taught or encouraged the person of ordinary skill in the art to provide compositions for administration via the eye or nose.

Finally, a person of skill in the art would not have been motivated to make the combination of Conte with Clancy, nor would he have had a reasonable expectation that the combination would be successful. Clancy is specifically concerned with producing compositions suitable for controlled drug release following oral administration. Moreover, none of the Clancy formulations contain fexofenadine. As would have been known to a person of skill in the art, the conditions in the stomach and other areas of the gastrointestinal tract are significantly different from those in the eye or nose. Thus, there is nothing in Clancy to suggest that the controlled release means described in Clancy would have been suitable for controlling the release of a drug administered through the nose or the eye. A person of skill would hot have been motivated to combine it with Conte.

For the reasons given above, it is respectfully submitted that the Examiner reconsider and withdraw all rejections under 35 U.S.C. § 103.

B. Secondary Considerations

For the reasons discussed above, the Examiner has failed to make a *prima facie* case of obviousness. However, assuming *arguendo* that the Examiner had mad a *prima facie* case, the case would be rebutted by the surprising and unexpected results achieved by the invention.

The chemical structures of terfenadine and fexofenadine are different (*See* section II, *supra*). A person of skill in the art at the time the invention was made would have understood that compounds of differing chemical structures exhibit different solubility behaviors in the same environment, even, in some cases, where the structural difference may appear minor. Thus, the behavior of terfenadine cannot be considered to be a predictor of the behavior of fexofenadine, under known scientific principles. The data submitted herewith in the Declaration of Peter James Watts (hereinafter "Watts Decl.") demonstrates that one of skill would not have been able to predict or extrapolate the solubility of fexofenadine in a given environment based upon the behavior of terfenadine in that same environment and, moreover, given the minimal solubility of terfenadine in the prior art compositions, a person of skill would not have been motivated to modify the prior art compositions to use fexofenadine. Watts Decl. at ¶ ¶ 11 to 16 (attached hereto).

An evaluation of the comparative solubilities of fexofenadine hydrochloride and terfenadine in aqueous solutions of hydroxylpropyl-β-cyclodextrin (HP-β-CD) was conducted by the inventor, Dr. Watts. *Id.* at ¶ ¶ 10 to 11. Solutions of fifty, twenty-five, and ten mg/ml HP-β-CD were used. *Id.* at ¶ 10. As can be seen in Table 1 and Figure 1 of the Watts Declaration, use of the various HP-β-CD solutions (as suggested in the prior art) facilitates a relatively small increase in solubility of the drug terfenadine. Watts Decl. at ¶ 11 (Table 1; Fig. 1); *see also id.* at ¶ ¶ 12-14 (comparative solubility evaluated in water, hydrochloric acid solution and ethanol). In contrast, a marked increase of fexofenadine solubility in the same solutions is demonstrated. *Id.* at ¶ 11 (Table 1; Fig. 1); *see also id.* at ¶ ¶ 12-14.

Accordingly, as the differing chemical structures of fexofenadine and terfenadine contribute to the differing solubility behaviors of each chemical, a person of skill in the art would not have been motivated to rely upon references teaching use of a cyclodextrin to increase the solubility of terfenadine to arrive at the present invention for any increase of solublilities could not be relied upon as predictive and the solubility increase was fairly minimal. The results are surprising and unpredictable, and demonstrate the non-obviousness of the present invention. Consequently, should the Examiner have established a *prima facie* case, the case would have been rebutted.

IV. Other Matters

At page 6 of paper no. 14, the Examiner has commented on the use of "(tetraglycol)" in the claims. The claims have been amended to remove the parenthetical reference. Accordingly, it is submitted that the Examiner's comment has been addressed and the claims are not in a from for allowance.

CONCLUSION

In view of the foregoing, it is respectfully submitted that pending claims 7, 20, 21, and 28-39 are distinguishable over the cited prior art. Reconsideration and allowance of the claims at the earliest opportunity is respectfully solicited.

Respectfully submitted,

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Enclosures:

Petition for a One Month Extension of Time for Response
Declaration of Peter James Watts (executed)
The Merck Index, 11th ed. at 1443

Amendments to and Listing of the Claims:

1. to 6. (Cancelled)

7. (Previously presented) A composition as claimed in claim 34, wherein the cyclodextrin is hydroxypropyl-β-cyclodextrin.

8. to 14. (Cancelled)

15. to 19. (Cancelled)

20. (Currently amended) A method of treating a patient in need of treatment with fexofenadine or a pharmaceutically acceptable salt thereof which comprises administering an effective amount of a composition according to claim 34 to an eye or nose of a patient in need of such treatment.

21. (Currently amended) A method of treating rhinitis which comprises administering an effective amount of a composition according to claim 34, to an eye or nose of a patient in need of such treatment.

22. to 27. (Cancelled)

28. (Previously presented) The composition as claimed in claim 34, which further comprises a gelling agent or a bioadhesive material.

29. (Previously presented) The composition as claimed in claim 28, wherein the gelling agent or bioadhesive material is selected from the group consisting of pectin, alginate, starch, gellan, chitosan, and a block co-polymer.

30. (Previously presented) The composition as claimed in claim 35, which further comprises a material that provides for controlled release of the fexofenadine or a pharmaceutically acceptable salt thereof.

31. (Currently amended) A method of treating a patient in need of a treatment with fexofenadine or a pharmaceutically acceptable salt thereof, the method comprising administering an effective amount of the composition according to claim 35 to an eye or nose of a patient in need of such treatment.

32. (Currently amended) A method of treating rhinitis, the method comprising administering an effective amount of a composition according to claim 35 to an eye or nose of a patient in need of such treatment.

33. (Previously presented) A method of treating a patient with a controlled release dose of fexofenadine or a pharmaceutically acceptable salt thereof, the method comprising administering an effective amount of a composition according to claim 30 to a patient in need of such treatment.

34. (Presently Amended) A composition consisting essentially of

(i) fexofenadine or a pharmaceutically acceptable salt thereof and

(ii) a pharmaceutical excipient that increases the solubility of the fexofenadine or salt in water selected from the group consisting of a cyclodextrin, propylene glycol, and glycofurol ~~(tetraglycol)~~,

which composition is adapted for delivery of the fexofenadine or pharmaceutically acceptable salt thereof to the eye or nose.

35. (Presently Amended) A composition comprising

(i) fexofenadine or a pharmaceutically acceptable salt thereof in an amount selected from the group consisting of 100 μg/ml to 100 mg/ml and 0.5% to 40% wt/wt and

(ii) a pharmaceutical excipient that increases the solubility of the fexofenadine or salt in water selected from the group consisting of a cyclodextrin, propylene glycol, and glycofurol ~~(tetraglycol)~~,

which composition is adapted for delivery of the fexofenadine or pharmaceutically acceptable salt thereof to the eye or nose.

36. (Previously presented) The composition of claim 35, wherein the cyclodextrin is hydroxypropyl-β-cyclodextrin.

37. (Previously presented) The composition of claim 35, wherein the composition further comprises an aqueous vehicle.

38. (Previously presented) The composition of claim 28, wherein the gelling agent or bioadhesive material is a polysaccharide.

39. (Previously presented) The composition of claim 29, wherein the block co-polymer is a poloaxmer.